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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,276	05/12/2000	Neal L. First	96429/9085	6126

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/463,276	FIRST ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application filed May 12, 2000, is a 371 national stage filing of PCT/US98/15387, filed July 24, 1998.

Applicants' amendment filed April 6, 2004, has been received and entered. Claim 4 has been canceled. Claim 13 has been amended. Claims 1-3, 5-14 are pending and currently under examination.

Claim Rejections - 35 USC § 102 and 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Gurdon (J. Cell. Sci., 1986 IDS reference).

Applicants note that the recipient oocyte in Gurdon was from an amphibian and does not teach the specific use of a bovine oocyte. Applicants argue that the intraspecies nuclear transfer taught by Gurdon is not the same as the trans-species nuclear transfer taught in the instant specification and does not anticipate an embryo with bovine cytoplasm and non-bovine DNA (top of page 5). Applicants argue that the embryos of claims 12 and 14 would be distinguishable because they would have cytoplasm and nuclear material with different characteristics noting that the bovine oocyte would have mitochondrial DNA that is different from that of the inserted nuclear material citing evidence from the cloning of Dolly in support of their arguments (bridging pages 5-6). Applicants' arguments have been fully considered but not found persuasive. It is noted that the products are products by process, however there is no recitation in the claim nor requirement of practicing the method as asserted by Applicants that the resulting embryo have components of bovine cytoplasm and non-bovine nuclear material. Initially, it is noted that Gurdon teaches that interspecies nuclear transfer was reduced to practice earlier that 1986 prior to the filing date of the instant application (see page 302). Further, Examiner acknowledges the results from the analysis of Dolly however these results are from **intra**species nuclear transfer, not **inter**species nuclear transfer as instantly claimed. Importantly, a resulting embryo will not be viable if the mitochondrial DNA and nuclear DNA are not complementary

and compatible in providing all the required mitochondrial proteins to produce a functional mitochondria. The results of Dolly demonstrate that mitochondrial DNA from the same species are complimentary and that the oocyte michondria can/will be present in a cultured embryo. However, as recognized in the art the mitochondria from a species different from the species of the nuclear material will not support a viable cultured cell, and most likely any resulting viable cultured cell will have mitochondria that is the same as the nuclear material that was introduced during the electrofusion of the nucleus/cell donor and the oocyte. It is noted that both claims 1 and 13, the methods claims from which the products depend both recite that the cells and oocytes are fused. There is nothing in the claims that the cytoplasmic factors present in the initial fusion are present after culturing the cell through the maternal-embryonic transition. To the contrary, because of the requirement of complimentary mitochondria and nuclear DNA the art would predict that the bovine cytoplasmic factors would be lost because the embryonic factors would first be made by the non-bovine nuclear genome, therefore the bovine proteins will be lost due to turnover and cell division. Second, any bovine mitochondria will be lost because the mitochondria proteins are encoded by the non-bovine nuclear material and the bovine mitochondria present at the initial fusion will be lost due to turnover, cell division or cell death due to the non-complimentary nature of the mitochondria and the nuclear material. Thus, any viable cell making the maternal-embryo transition will have selected mitochondria that is compatible with the nuclear material, not bovine mitochondria. Applicants have asserted that the resulting cell will be distinguishable because it will contain bovine cytoplasmic factors and non-bovine nuclear material, however this assertion is not supported by any evidence of record and is contrary to the skilled artisans expectation of a cell that has undergone the embryonic transition.

Again, Examiner would concede that Gurdon does not reduce to practice the methods instantly claimed, thus the specific embryos instantly claimed, however, Gurdon clearly discusses nuclear transfer in species other than amphibians noting the early success of nuclear transfer in mammals (page 312, citing the work of Hoppe, Illmensee, Kelly and McGrath). Further, in the description of nuclear transfer between species, the experiments proposed focus on the analysis of affects on development of maternal factors and chromosomal factors (pages 301-302) indicating that the cultured NT unit is generated and cultured for analysis of the embryonic to maternal transition. Gurdon specifically discusses the state of the art for mammalian nuclear transfer and provides an example wherein the nuclear material was from a mammal. Because a bovine is a mammal, and transpecies nuclear transfer would encompass the use of a bovine oocyte and nuclear material from a cell other than a bovine, the teachings of Gurdon anticipate, or make obvious the instantly claimed embryos. In view of the teachings of the reference as whole, clearly the generation of other trans-species combinations, *i.e.* nuclear material of one species into a mammalian oocyte, for the study of development would be encompassed by the teachings of Gurdon.

Applicants argue that the claimed products would not be obvious under 35 USC 103 because of the differences between the transition states of amphibians, sheep, swine, and rodents known in the art would not predict success of the claimed methods (page 6). These arguments are not found persuasive, because these differences were known at the time of filing. While each amphibians, sheep, swine, and rodents do not exactly capitulate the exact timing of the embryological steps they were/are studied and compared as models of embryological development. As noted by Applicants, the art recognizes the differences in the specific nature of

development of embryos of different species. In addition, Examiner notes the results of Brun as cited by Gurdon, and beyond evidence that may support arguments provided above for the requirement of complimentary mitochondria and nuclear DNA this is one example that would be considered outside the scope of the claims as non-enabled because as noted by Applicants the embryos were viable only through a few cell divisions. Though it is not evidence that the resulting embryo did not make the maternal-embryonic transition, Examiner would agree that such a cell would be non-viable, however it is unclear from the general teachings of the instant specification how the methodology differs. Moreover, this distantly related trans-species experiment is representative of the complimentary embodiment of a bovine oocyte and amphibian nuclear material encompassed by the claim. Applicants arguments are not found persuasive because the differences noted by Applicants were known in the art at the time of filing are also representative of limitations encompassed by the instantly claimed methods. The present specification provides no specific guidance to what combinations will or will not work, and by omission supports that any species combination should work.

Claims 12 and 14 stand rejected under 35 U.S.C. 102(e) as being anticipated by Stice *et al.* (WO 95/17500).

Applicants argue as above the resulting embryo will have cytoplasmic characteristics of bovine and nuclear characteristics that are non-bovine (top of page 7). Further, it is argued that Stice *et al.* does not teach trans-species nuclear transfer, and that the chimeric animals discussed are of the same species (bridging pages 7-8).

Examiner acknowledges that the term chimeric is not defined by Stice *et al.*, however what is relied upon in the teaching of Stice *et al.* is embryos made by nuclear transfer that have made the maternal-embryonic transition. As discussed above, such a cell would be viable only if the nuclear and mitochondrial DNA are complimentary. Thus, one resulting product of practicing the method of either claims 1 or 13 is an embryo that is the same as an nuclear transfer embryo of the same species. Moreover, the instantly claimed products would be anticipated by an embryo produced by IVF or even by natural means. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972) . Applicants arguments that the claimed products would be distinguishable from that of Stice *et al.* are not persuasive because there is no evidence in support of this assertion. Moreover, the products as claimed do not recite nor require any specific physical limitations beyond that the embryo has made the maternal-embryonic transition, thus any embryo making this transition anticipates the instantly claimed product.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Prather *et al.* (Biology of Reproduction, 1987, IDS reference), Gurdon (J. Cell. Sci. , 1986), Campbell *et al.* (WO 97/07668, March 1997, IDS reference), Telford *et al.* (Molecular Reproduction and Development, 1990, IDS reference), Dominko *et al.* (Molecular Reproduction and Development, 1997, IDS reference) in further view of Stice *et al.* (WO 95/17500)

Applicants summarize the requirements of making a rejection under 35 USC 103, citing MPEP 2143 in support. Applicants arguments appear to focus on the fact that none of the cited references specifically teach to use a bovine oocyte, and the evidence presented in Gurdon do not provide an expectation of success (pages 8-10). Applicants' arguments have been fully considered but not found persuasive.

Applicants are arguing that the cited references do not expressly suggest the claimed invention however, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67

(CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Further, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). In this case, Examiner agrees with Applicants analysis of Gurdon that the results using amphibian oocyte would not specifically predict the outcome for the use of bovine oocyte as a recipient. However, the teaching of Gurdon is not so simple as to only indicate the effectiveness of using amphibian oocyte in transspecies nuclear transfer. Rather, Gurdon teaches that the more related the oocyte recipient/nuclear transfer unit species is phylogenetically, the better able is the resulting NT unit to be cultured. The instant claims are broad encompassing the use of any non-bovine nuclear material in generating the NT unit. The bovine oocyte, like the amphibian oocyte has certain capacities to support growth of a NT unit made by transpecies nuclear transfer.

Examiner agrees with Applicants analysis of Gurdon that the results using amphibian oocyte would not specifically predict the outcome for the use of bovine oocyte as a recipient. However, the teaching of Gurdon is not so simple as to only indicate the effectiveness of using amphibian oocyte in transspecies nuclear transfer. It should be noted that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC

1988). Here, Gurdon teaches that the more related the oocyte recipient/nuclear transfer unit species is phylogenetically, the better able is the resulting NT unit to be cultured. This is not using the specification as a blueprint, it is a conclusion of Gurdon based on the evidence known in the art. Furthermore, it should be noted that the instant claims are broad encompassing the use of any non-bovine nuclear material in generating the NT unit. The results of discussed in Gurdon represent the compliment of using a bovine oocyte and any other species of nuclear donor. As acknowledged by Applicants it was recognized that different species, like the results specific presented for the amphibian oocyte, have certain capacities to support growth of a NT unit made by transpecies nuclear transfer.

As discussed above to the extent that an amphibian oocyte will only support the prolonged growth in culture of certain nuclear donors, Examiner would agree that the use of amphibian oocyte with a different nuclear material would not be absolutely predictive of using bovine oocyte with the same nuclear material however, the results and teachings of Gurdon clearly would lead the artisan to predict and expect that the closer the species relationship of the donor and recipient, the more viable the resulting NT would be. Gurdon teach that transpecies nuclear transfer has been attempted for a wide variety of species of animals, and in view of the teachings of the reference as a whole provides for the use of recipient mammalian oocyte. S

Applicants do not contest nor argue that the specific method steps are not anticipated by the cited references, only that there is no specific teaching to use a bovine oocyte and that using a bovine oocyte as a recipient one would have an expectation of success. This is not found convincing because the claimed methodology for nuclear transfer and culturing of the resulting embryos as instantly claimed is taught in both Prather *et al.* and Stice *et al.* and is very analogous

in all references, indicating that the conditions used by the artisan to generate and culture non-chimeric embryos would at least initially used for chimeric embryos. Campbell *et al.* provides a recent status of nuclear transfer techniques, and in particular, Campbell teaches the use of donor cells which have been arrested in Go by various methods, maturation curves of the bovine oocyte, and activation of the NT unit by various techniques known in the art. Further, Campbell teaches that the described nuclear transfer technology can be used to generate transgenic animals as well (entire reference; summarized in abstract and specifically claimed). Additionally, Dominko *et al.* and Telford *et al.* both provide further guidance for the optimization of in using bovine oocyte known in the art at the time of filing. Specifically, Dominko *et al.* demonstrate that there is an increased efficiency in embryo development when the genetic material is transferred later that 8 hours of culturing (Figures 3 and 4). Examiner concedes that Telford *et al.* teach that there is a transition from maternal control (donor oocyte control) to the embryo for various species of animals and in particular, in the cow, this change occurs between 8-16 days. However, Stice et al. teaches that embryos that activation for most domestic animals will range from 16-52 hours (page 23; lines 16-27). In view of the work of Stice *et al.* and Dominko *et al.* it is clear that to establish the control of the genetic material transferred by nuclear transfer techniques, at least in the bovine, the artisan would deliver the nuclei after the 16 hour culture transition period.

A review of the teaching of the present specification does not indicate that optimization for use of a bovine oocyte would be subject to the species of nuclear material introduced, only that a bovine oocyte should be used. It is maintained that in view of the art as a whole, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention

was made to generate chimeric embryos by nuclear transfer techniques. As noted in Gurdon cross-species nuclear transfer has been performed for prior to the time of the claimed invention, however it was also observed that optimization of the methods would be necessary. Campbell *et al.*, Telford *et al.* and Dominko *et al.* provide such optimization conditions detailing specific method steps and materials necessary to increase embryo development for the cow. One of skill in the art would have been motivated to use the teachings of Campbell *et al.*, Telford *et al.* and Dominko *et al.* because at the time of the claimed invention they represented the latest and best conditions/methods available to practice nuclear transfer techniques.

Thus, the claimed invention, as a whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach